REMARKS

Claims 1-6, 8-17, 19, 21-93 are pending, claims 7, 18 and 20 having been cancelled and new claims 84-93 having been added by the present amendment. Claims 16 and 53-82 are withdrawn from consideration. Claims 1-6, 8-10, 14-15, 17, 19, 25-28, 31-32, 34, 41, 45, 47, 51-52 and 83 have been amended. In some cases, the amendments merely correct typographical or grammatical errors. Support for the other amendments and new claims is provided throughout the application. For example, support for a small peptide "other than somatostatin" can be found, e.g., on page 52, lines 21-24; support for a pro-region "sufficient to promote secretion from a cell" and "secreting" a peptide can be found, e.g., on page 59, lines 5-12; support for variants of the pro-region having between one and 15 residue differences from wild type can be found, e.g., in the paragraph bridging pages 59-60; support for "non-endocrine cell" can be found, e.g., on page 6, line 1; and pages 61-62. Support for "homologously recombinant cell" is found, e.g., at page 10, lines 17-29, and page 62, lines 1-11. Support for a "fusion protein" can be found, e.g., on page 1, lines 17-18 and original claim 20, now canceled. No new matter has been added.

Claims 1-6, 8-15, 17, 19, 21-52 and 83-93 are under examination.

The Invention

The invention is based on the discovery that, by fusing the pro-region of somatostatin to a small peptide other than somatostatin, the small peptide can be secreted from a cell that does not normally secrete the small peptide (such as a non-endocrine cell). The claims cover constructs that include nucleotide sequences encoding (a) a signal peptide, (b) the pro-region of somatostatin (or a functional fragment of or analog thereof sufficient to promote secretion from a cell), and (c) a small peptide other than somatostatin; and a non-endocrine cell (and related methods of making the cell or making a small peptide from the cell) where the cell produces a subject small peptide fused to a functional pro-region of somatostatin.

Restriction Requirement

The Examiner has made the restriction requirement final. Applicants reserve the right to Petition the Commissioner to review the requirement under 37 C.F.R. § 1.144.

Objections and Rejections Under 35 U.S.C. §112, Second Paragraph

Claims 1-15, 17-52 and 83 are rejected under 35 U.S.C. §112 as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Each aspect of this rejection is addressed in turn below.

The Examiner states that claims 1 and 14 are indefinite for recitation of "a functional fragment or analog" of the pro-region of somatostatin. Applicants submit that the meaning and scope of the term would be clear to one of ordinary skill in the art given the guidance in the specification. However, in order to expedite prosecution, this rejection has been addressed by amending the claims to specify that a functional fragment or variant of the pro-region of somatostatin differs from the wild-type sequence by at least 1 but not more than 15 amino acid residues, wherein the variant is sufficient to promote secretion from a cell. New claims 90-93 recite even narrower limitations on the variant. This amendment is supported, e.g., at page 59, lines 6-12; and page 59, line 27 to page 60, line 17, of the specification. Given the guidance in the specification, it would be trivial to make and use such functional variants of the pro-region of somatostatin. As discussed at pages 59-60, routine techniques can be used to create variants that differ from the wild type by the parameters recited in the claims. The ability of the pro-region to promote secretion of a linked polypeptide from a cell is easily tested using the methods set out in the specification, e.g., in Example 2.

Claims 2, 6, 7, 17, 18, 28, 45, 47, and 51 are rejected as indefinite for the recitation of "the nucleic acid sequence...is from the pro-region" as the term "pro-region" is used to specify and amino acid sequence. This rejection has been met by amending the claims to recite "a nucleic acid sequence encoding..." where appropriate.

Claims 6, 8, 17 and 32 are rejected as indefinite with regard to "a site." The claims have been amended to specify that the site is a cleavage site in the encoded protein, thereby overcoming the rejection. The amendments are supported, e.g., by claims 7 and 18, now canceled.

Claim 9 is rejected as unclear. The phrase "end protease cleavage site" has been amended to recite "endoprotease cleavage site," thereby obviating the rejection. This

amendment merely corrects an obvious typographical error (see for example, original claims 33 and 64, now withdrawn).

Claim 14 is rejected as indefinite for failing to specify the relationship between the exogenous nucleic acid sequence and the sequence encoding the small peptide. This rejection has been met by amending claim 14 to specify that the cell encodes a fusion protein that includes the three specified components: a signal peptide, a pro-region of a somatostatin or a functional fragment or analog thereof, and a small peptide other than somatostatin. Support for this amendment can be found, e.g., at page 1, lines 17-19; and page 13, lines 14-16, of the specification.

Claims 19 and 39 are rejected as indefinite for recitation of a "mature form." The Examiner states "a mature form of a peptide varies depending on the cell type used to express the peptide. As such, the metes and bounds of the claim cannot be unambiguously determined." Applicants respectfully traverse this grounds for the rejection. It would be clear to an ordinary skilled artisan guided by the specification that the "mature form" of the small heterologous small peptide is the small peptide having been cleaved from the pro-somatostatin sequence. See, e.g., page 2, lines 15-16; page 7, lines 13-14; page 12, lines 28-29; and page 17, lines 10-11 of the specification.

Claim 36 is rejected for lack of antecedent basis for "the cleavage site." The base claim (claim 18) has been amended to correct this technical error.

Claim 41 is rejected as indefinite for having two phrases directed to "a small peptide". This rejection has been met by amending the second phrase to read "the small peptide."

Claim 47 is rejected as unclear for failing to specify whether the nucleic acid sequence encoding the pro-region is linked to the nucleic acid encoding the small peptide prior to, or as a result of, the "introducing." Claim 47 has been amended to indicate that the linkage is a result of homologous recombination of the exogenous DNA and the genome of the cell. Support for this amendment can be found, e.g., at page 26, lines 1-5; and page 62, lines 6-11, of the specification.

Claim 83 is rejected as indefinite for failing to provide a structural relationship between the elements. This aspect of the rejection has been addressed by amending claim 83 to recite that the nucleic acid sequence encodes a fusion protein that includes the recited elements. Support for

this amendment can be found at page 1, lines 17-20; page 3, lines 3-5; page 13, lines 14-16, of the specification.

In view of the foregoing, Applicants submit that the meaning and scope of the present claims would be clear to a skilled artisan. Therefore, withdrawal of the rejection is respectfully requested.

Objections and Rejections Under 35 U.S.C. §112, First Paragraph

Enablement

Claim 15 is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in such a way as to enable one skilled in the art to make the invention. The Examiner states "neither the claim, nor the specification provides specific information as to how the exogenous and the endogenous sequences are related, and how one affect the other regarding the expression of the small peptide. Additionally, the specification provides no guidance or working example as to how to make such a cell." The Examiner concludes that "due to the large quantity of experimentation necessary to determine how to make the claimed cell, the lack of direction/guidance presented in the specification regarding same, the complex nature of the invention, undue experimentation would be required of the skilled artisan to make the claimed invention."

The rejection has been addressed, in part, by amending claim 15 to clarify the relationship among the elements of the cell. This rejection is respectfully traversed insofar as it may be applied to claim 15 as presently amended. As amended, claim 15 covers a non-endocrine cell that includes a nucleic acid sequence that encodes a fusion of a signal peptide, a pro-region of a somatostatin (or a functional fragment or variant as recited), and a small peptide other than somatostatin, where the small peptide portion of the fusion protein is encoded by an endogenous genomic sequence and the cell is a homologously recombinant cell.

At the outset, the Examiner is reminded that a working example is not required to enable the claim. Nor need Applicants have actually made the cell of claim 15. The claim is enabled if an ordinary skilled artisan can make and use the claimed cell without undue experimentation. The specification, combined with the knowledge and skill in the art, clearly provides sufficient guidance for making and using the claimed cells. See, for example, page 10, lines 16-29; and

page 62, lines 1-11, where the specification provides art-recognized methods of making the claimed cells, e.g., referencing (and incorporating by reference) U.S. Patents No.: 5,641,670 and 5,733,761 for specific methodology. In particular, the referenced patents describe art-recognized methods of activating expression of an endogenous gene, whereby an exogenous nucleic acid sequence is introduced into a cell (e.g., by homologous recombination) such that the exogenous sequence is linked to an endogenous nucleic acid sequence encoding a subject protein. This method (generally called "gene activation") turns on an endogenous gene in a cell. The method is neither unpredictable nor undeveloped. In fact, therapeutic products made by this method were in use at the time of filing. For example, gene activated erythropoietin (GA-EPO) was in Phase III clinical trials at the time of priority of the present application (see attached Press Release). Thus, to make the claimed cell, a skilled artisan could readily use the guidance provided in the specification and the knowledge in the art to transfect a cell with an exogenous nucleic acid that encodes a signal peptide and the pro-region of somatostatin (in addition to an exogenous regulatory sequence and targeting sequence as described in the referenced patents) such that the exogenous nucleic acid would recombine with the endogenous nucleic acid sequence encoding the small peptide to make the fusion as recited in the claims. Accordingly, claim 15 is enabled and Applicants respectfully request that this rejection be withdrawn.

Written Description

Claim 15 is further rejected as containing subject matter which was not described in the specification in such a way as to reasonably convey that the inventors had possession of the claimed invention. The Examiner states that "no such cell meeting the limitations of the claim is identified or particularly described in the specification." The Examiner cites Fiers v. Revel (25 USPQ 2d 1601) and Amgen v Chugai (18 USPQ 2d 1016) in support of the proposition that "conception is not achieved until reduction to practice has occurred." This rejection has been met, in part, by amending claim 15 (and claim 14, from which claim 15 depends) to add additional limitations in order to more specifically describe the claimed cell. However, the Examiner's specific grounds for rejection are traversed, in part, for at least the following reasons.

Amgen and its progeny stand for the proposition that, absent structural information, the claiming of a DNA, by mere function, does not satisfy the written description requirement. Fiers held:

> We thus determined that, irrespective of the complexity or simplicity of the method of isolation employed, conception of a DNA, like conception of any chemical substance, requires a definition of that substance other than by its functional utility. (Fiers at 1169, emphasis added.)

Thus, both of the cited cases relate to written description as it applies to undescribed, previously unknown nucleic acid sequences or chemical compounds. The Examiner's reasoning demands the same result when the written description standard is applied to the very different fact pattern of the present invention. In sharp contrast to Amgen, the present invention lies in the novel way that known and readily available sequences (sequences encoding (a) a signal peptide, (b) a pro-region of somatostatin and (c) a small peptide) are specifically selected and arranged in the claimed constructs, cells and methods to achieve a novel result, i.e., the secretion of a small peptide other than somatostatin. Claim 15 claims a cell, not a DNA or chemical substance. The claimed cell is amply described in terms of specific distinguishing, identifying characteristics. These include being a homologously recombinant cell, containing known and readily available sequences, the sequences having a particular and specific arrangement in the cell. Thus, a skilled artisan could readily visualize and recognize the full scope of the claimed cells. Claim 15 is sufficiently detailed to show that applicant was in possession of the invention, as required by the standard of Vas Cath. Accordingly, withdrawal of the rejection is therefore requested.

Rejections Under 35 U.S.C. §102(b)

Claims 1-4, 6-10, 12, 14, 17-20, 22, 23, 26-30, 32-34, 38-41, and 43-45 are rejected under as anticipated by Sevarino et al. (Cell, 1989, 57(1):11-19). Sevarino describes a construct (and endocrine cells containing the construct) that encodes a chimera of the rat somatostatin signal peptide and proregion fused to the C-terminus of anglerfish somatastatin. Thus, the "small peptide" of the Sevarino constructs and cells is a somatostatin peptide. The

This rejection has been addressed by amending claims 1 and 14 (from which all the rejected claims depend), to explicitly recite that the small peptide is other than somatostatin.

This amendment is supported throughout the application, e.g., at page 52, lines 21-24. Accordingly, Sevarino does not anticipate the present claims.

Applicants respectfully request that the rejection be withdrawn.

Rejections Under 35 U.S.C. §103(a)

Claims 5, 9, 11, 13, 31, 35, 37, 46, 52, and 83 are rejected under 35 U.S.C. §103(a) as unpatentable over Sevarino in further view of Stoller, Habener, Susuki and Patel. Sevarino discloses a construct encoding a chimera of the pre-pro region of a rat somatostatin and the C-terminus of anglerfish somatostatin, expressed in AtT20 and RIN 5F cells (both endocrine secretory cell lines). Stoller describes a construct encoding a chimera of the pre-pro region of somatostatin and α-globin expressed in rat pituitary tumor (endocrine) GH3 cells. Habener teaches that GLP-1 is a potential therapeutic agent for treatment of diabetes and teaches production of GLP-1 by "conventional means such as by the well-known solid-phase peptide synthesis...by fragmenting the naturally occurring amino acid sequence, using for example, a proteolytic enzyme...or through recombinant DNA technology" (column 4, line 68-column 5, line 12 of Habener et al.). Susuki describes a method for producing a chimeric protein that can be cleaved and efficiently produced as an inclusion body in *E. coli* under large scale culture (Susuki 2:6-11). Patel teaches that mammalian pro-protein convertases such as furin, PACE4, and PC1-6, mediate endoproteolysis of prosomatostatin.

The Examiner provides the following grounds for the rejection:

> The person of ordinary skill in the art would have been motivated to make the construct and the host cell for expressing GLP-1 because of the potential therapeutic application of GLP-1 in treating diabetes as suggested by Habener, the advantage of using the pro-region of somatostatin in targeting the hormone peptide as taught by Sevarino and Stoller, and the advantage of using the prohormone processing enzymes such as furin for cleaving the chimeric peptide in order to remain the peptide undamaged as taught by Susuki, and reasonably would have expected success because Sevarino and Stoller have demonstrated successful expression of two different heterologous peptides by using fusing pro-region of prosomatostatin with the target peptide, and the prior art has established that when a processing enzyme such as furin is used for excising a target peptide from the [chimeric] protein, the peptide hormone is not damaged, as indicated by Susuki.

With regard to claims 31, 35, 37, 46 and 52, this rejection has been met by amending the base claims 14, 41 and 47 to recite that the claimed cell is a non-endocrine cell, thereby similarly limiting the rejected claims. None of the cited references, alone or in combination, teach or suggest a non-endocrine cell that expresses a fusion of the pro-region of somatostatin with any small peptide, much less GLP-1 or any other peptide specifically recited in the claims.

At most, the references suggest that the pro-region of somatostatin could be used to promote regulated secretion in endocrine (hormone producing) cells, i.e., the type of cell in which somatostatin is normally expressed. Endocrine cells use very specific mechanisms for secretion of proteins. There is no suggestion in the art that the pro-region of somatostatin would function in a non-endocrine cell.

In particular, Sevarino and Stoller both investigated the role of the somatostatin propetide in mediating targeting to the regulated secretory pathway of hormone secreting cells (i.e., endocrine cells), in particular AtT20, RIN 5F and GH3 cells. Both references conclude that the pro-region of somatostatin is important for mediating regulated secretion in endocrine cells, but say and suggest nothing about a role for the somatostatin propetide in cells that do not normally undergo regulated secretion of hormones, i.e., in non-endocrine cells. Thus, these references provide no motivation, and certainly no expectation of success, for a skilled artisan to express a pro-region of somatostatin fused to a heterologous polypeptide (much less a heterologous small peptide specifically) in a cell that does not undergo regulated secretion. Indeed, Stoller suggests that the role of the somatostatin propetide in endocrine secretion is specific to regulated secretion in hormone producing cells. Stoller states:

> Peptide hormone-producing cells characteristically concentrate and store their secretory product in electron dense secretory granules. Upon stimulation by an extracellular signal, these granules fuse, through a calcium-dependent process, with the plasma membrane releasing their contents into the external milieu. This type of secretion is designated "regulated" or "stimulated". Hormone secreting cells also undergo basal or "constitutive" secretion whereby nonhormone secretory proteins and plasma membrane proteins are neither concentrated nor stored and are transported into vesicles which continuously fuse with the plasma membrane in a calcium-independent manner. Since hormone-secreting cells undergo basal secretion, a mechanism must exist that discriminates between molecules destined for the regulated or constitutive pathways (page 1647, right column)

Based on experiments showing that the pro-region of somatostatin mediated transport of α-globin to the regulated pathway in an endocrine cell (i.e., the type of cell in which somatostatin is normally expressed), Stoller concludes that the pro-region of somatostatin is the mechanism by which molecules specifically destined for the regulated pathway of endocrine cells are sorted. No role of the pro-region in constitutive secretion (the type of secretion exhibited by non-endocrine cells) is suggested or contemplated.

None of the remaining references (Patel, Habener and Susuki) make up for the deficiencies of the references discussed above, either alone or in combination. The references, even if combined, do not teach or suggest fusing the pro-region of somatostatin to a heterologous small peptide in a non-endocrine cell. If anything, Patel teaches away from the use of the pro-region of somatostatin to mediate secretion in non-endocrine cells. In particular, Patel notes the highly inefficient cleavage of prosomatostatin to somatostatin in non-endocrine cell types such as PC-12 and COS-7. Referring to Figure 2, Patel states:

> PC-12 cells were similar to COS-7 cells in that they exhibited inefficient constitutive processing of prosomatostatin. . . .In contrast to COS-7 and PC-12 cells, AtT-20 [endocrine] cells not only targeted prosomatostatin-derived peptides to the regulated secretory pathway but also processed prosomatostatin efficiently. (Patel, page 31, referring to Figure 2.)

Given that about 60% of total prosomatostatin remained unprocessed in the non-endocrine cells COS-7 and PC-12 (compared to almost no unprocessed somatostatin in endocrine cells AtT-20 and GH3, see Figure 2), Patel does not provide a motivation or reasonable expectation of success to use the pro-region of somatostatin to promote processing and secretion of a heterologous small peptide in a non-endocrine cell, as recited in the claims. If anything, Patel's observations suggests that non-endocrine cells lack the proper machinery to efficiently process prosomatostatin, much less a chimeric peptide having the proregion linked to a heterologous peptide. Accordingly, claims 31, 35, 37, 46 and 52 are patentable over the cited references.

With regard to claims 5, 13 and 83 (which cover constructs for expression of specifically recited peptides, such as GLP-1) and claims 9 and 11 (which cover constructs with specific cleavage sites for cleavage of the small peptide from the pro-region), the rejection is respectfully

traversed. The cited references lack the requisite specific motivation and reasonable expectation of success to combine the references to arrive at the specific claimed constructs. The mere fact that references (in this case, five references) can be combined does not render the resultant combination obvious unless the prior art also evidences the desirability of the specific combination as claimed. See MPEP § 2143.01. In this case, the Examiner appears to have merely plucked limitations from numerous prior art references and pieced them together using the claims as a template. The Federal Circuit has made it clear that this is impermissible.

The Examiner cites Habener for providing a motivation to produce GLP-1. Applicants do not dispute that Habener teaches the potential therapeutic activity of GLP-1 in treating diabetes. However, the Examiner has not pointed to any specific motivation in any of the cited references, to combine the teachings of Habener with those of the other references, in such a manner as to arrive at the specific constructs for production of GLP-1 as recited in the rejected claims. The fact that producing GLP-1 might be desirable does not make any one specific method or construct for producing it obvious. The Examiner has provided no evidence of a specific motivation to produce the claimed constructs. A showing of a suggestion, teaching, or motivation to combine "must be clear and particular...Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" In re Dembiczack, 175 F.3d 994 (Fed. Cir. 1999). Thus, the Examiner's broad, generic basis for finding motivation is insufficient.

In addition, the Examiner supports the rejection by stating that one "reasonably would have expected success because Sevarino and Stoller have demonstrated successful expression of two different heterologous peptides by using fusing pro-region of prosomatostatin with the target peptide a nucleic acid sequence encoding a signal peptide." However, neither Sevarino's nor Stoller's results are predictive of whether one could successfully express a heterologous (non-somatostatin) small peptide, as claimed. Sevarino expressed a somatostatin from a different source than the pro-region, but a somatostatin nonetheless. Stoller demonstrated expression of a large polypeptide (globin). Neither of these references provides a reasonable expectation that expression of a heterologous small peptide would be successful. A skilled artisan would be aware, for example, that expression of small peptides involves different technical challenges (such as increased degradation) than expression of larger polypeptides such as globin. In

addition, the constructs have the surprising property that they allow expression in a non-endocrine cell.

In sum, the fact that various elements related to the claimed nucleic acids, cells, and methods have been noted in isolation does not render the invention obvious without a specific motivation to be found in the art to arrive at the specifically claimed constructs. The Examiner has not provided such a specific motivation, or a reasonable expectation of success, as required in order to establish a *prima facie* case of obviousness. Accordingly, Applicants respectfully request that the rejection be withdrawn.

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TKT Announces Completion of Pivotal Phase III Renal Studies of Gene-Activated(TM) Erythropoietin .

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CAMBRIDGE, Mass., Jan. 11 /PRNewswire/ --

Transkaryotic Therapies, Inc.(Nasdaq: TKTX) announced today the completion of dosing for the pivotal Phase III clinical trials of Gene-Activated(TM) erythropoietin (GA-EPO(TM)) in the United States and United Kingdom by its partner, Aventis Pharma, the pharmaceutical company of Aventis S.A. (NYSE: AVE). Longer term maintenance studies of certain Phase III GA-EPO clinical trials are ongoing. The studies were designed to assess the safety and efficacy of GA-EPO as a treatment for anemia of renal failure in dialysis and pre-dialysis patients and are intended to support filing for market approval in both the United States and United Kingdom. The data from the trials are being collected, and, if the results are positive, the filings of a Biologics License Application (BLA) to the U.S. Food and Drug Administration and a Marketing Authorization Application (MAA) to the European Medicines Evaluation Agency are expected in 2000.

Approximately 1,400 patients with renal failure participated in the Phase III studies. The Phase III program was comprised of clinical trials in the United States and United Kingdom to test GA-EPO as a treatment of anemia related to renal disease in patients who were receiving dialysis and in patients who had not yet undergone dialysis. In addition, the clinical program was designed to deliver GA-EPO by both intravenous and subcutaneous routes of administration. Aventis is responsible for the worldwide development and commercialization of GA-EPO. TKT will receive a low double- digit royalty on net sales of the product.

Furthermore, TKT announced that Aventis has filed an Investigational New Drug Application (IND) with the FDA to commence a Phase III clinical trial to study GA-EPO as a treatment for anemia associated with cancer chemotherapy. The Phase III trial is expected to be completed in 2000.

"Aventis designed a broad clinical program for GA-EPO to treat multiple indications associated with anemia including dialysis, pre-dialysis, and oncology," said Richard F Selden, M.D., Ph.D., President and Chief Executive Officer of TKT. "We believe that following review by regulatory authorities, GA-EPO has the potential to serve all major

indications in the $4 billion erythropoietin market."

Transkaryotic Therapies, Inc. (TKT) is a biopharmaceutical company dedicated to the development and commercialization of products based on its three proprietary development platforms: Gene-Activated(TM) proteins, Niche Protein(TM) products, and Gene Therapy. The Company's gene activation technology is a proprietary approach to the large-scale production of therapeutic proteins, which does not require the cloning of genes and their subsequent insertion into non-human cell lines. TKT's Niche Protein product platform is based on protein replacement for the treatment of rare genetic diseases, a group of disorders characterized by the absence of certain metabolic enzymes. The Company's Gene Therapy technology, known as Transkaryotic Therapy(TM), is focused on the commercialization of non-viral, ex vivo gene therapy products for the long-term treatment of chronic protein deficiency states.

This press release contains forward-looking statements that involve a number of risks and uncertainties. For this purpose, any statements contained herein that are not statements of historical fact may be deemed to be forward-looking statements. Without limiting the foregoing, the words, "believes," "anticipates," "plans," "expects," "intends," and similar expressions are intended to identify forward-looking statements. Important factors that could cause actual results to differ materially from the expectations described in these forward-looking statements are set forth under the caption "Certain Factors That May Affect Future Results" in the Company's Quarterly Report on Form 10-Q for the quarter ended September 30, 1999 which is on file with the Securities and Exchange Commission and incorporated herein by reference. These important factors include risks as to whether TKT's products will advance in the clinical trials process, the timing of such clinical trials, whether the clinical trial results will warrant continued product development, and whether the Company's products will receive approval from the U.S. Food and Drug Administration or equivalent regulatory agencies, and, if such products receive approval, whether they will be successfully marketed.

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